TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: SANSYL006

U S APPLICATION NO. (If known, see 37 CFR 1.5): 10/031087

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/01994	11 July 2000	16 July 1999

TITLE OF INVENTION:
TITANIUM COMPOUNDS, PREPARATION AND USE THEREOF

APPLICANT(S) FOR DO/EO/US
FINIDORI, Claudine

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
    Citation of References
    Information Disclosure Statement by Applicant (Form PTO-1449)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031087	PCT/FR00/01994	SANSYL006

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO $1040.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$890.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ...$740.00
International preliminary examination fee (37 CFR 1.482)paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfy provisions of PCT Article 33(1)-(4).....$100.000

CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	29 -20 =	9	x $18.00	**$ 162.00**	
Independent claims	1 - 3 =	0	x $84.00	**$**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	**$**	
			TOTAL OF ABOVE CALCULATIONS =	**$ 1052.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
			SUBTOTAL =	**$ 1052.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$**	
			TOTAL NATIONAL FEE =	**$ 1052.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				**$**	
			TOTAL FEES ENCLOSED =	**$ 1052.00**	
				Amount to be refunded:	$
				Charged	**$1052.00**

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **19-0091** in the amount of **$ 1052.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **19-0091**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Patent Department
Sanofi-Synthelabo Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355
Facsimile: (610) 889-8799

PATENT TRADEMARK OFFICE

27546

PATENT TRADEMARK OFFICE

Michael D. Alexander 14 January 2002
SIGNATURE DATE

Michael D. Alexander
NAME

36,080
REGISTRATION NUMBER

(610) 889-8802
TELEPHONE NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International
Application No.: PCT/FR00/01994

Applicants: FINIDORI, Claudine

International Filing Date: July 11, 2000

For: TITANIUM COMPOUNDS, PREPARATION AND USE THEREOF

CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: EL676470460US

Date of Deposit: January 14, 2002

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Commissioner for Patents, Box PCT, Attn: EO/US, Washington, DC 20231.

Signature

Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Specification:

Please amend the specification as follows:

After the claims, please insert the following Abstract as new page 24 (a copy of which is enclosed herewith for the examiner's convenience).

ABSTRACT

The invention relates to a titanium-derived compounds, and to processes for preparing the same.

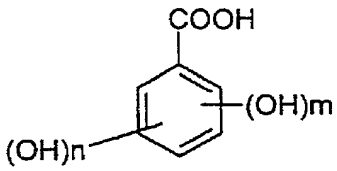
In the Claims:

Please amend claims 1-16, and add new claims 17-29 as follows before calculating the filing fee for the above-identified application.

1. (Amended) A titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:

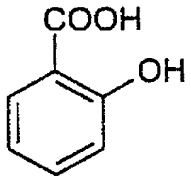


(II)

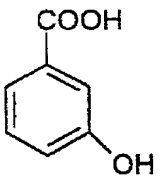
in which m is 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

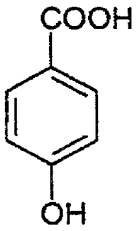
2. (Amended) A compound according to Claim 1, wherein the compounds L are chosen from benzoic acid derivatives, in particular 2-hydroxybenzoic acid of formula:



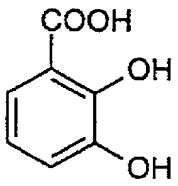
3-hydroxybenzoic acid of formula:



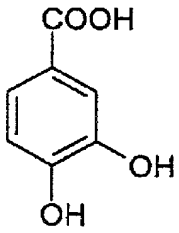
4-hydroxybenzoic acid of formula:



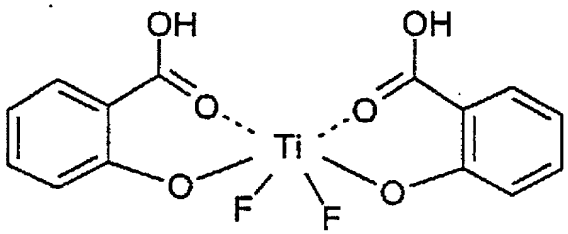
2,3-dihydroxybenzoic acid of formula:



3,4-dihydroxybenzoic acid of formula:



3. (Amended) A compound according to Claim 1, wherein it satisfies the formula below (III):



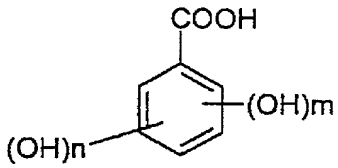
(III)

4. (Amended) A method for preparing a titanium-derived compound according to Claim 1 wherein solid titanium IV fluoride is reacted with a solution of benzoic acid in an anhydrous solvent such as acetonitrile, under a nitrogen atmosphere.

5. (Amended) A composition for buccal use, wherein it comprises at least one titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

in which m is 0, 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

6. (Amended) A composition for buccal use according to Claim 5 wherein it comprises at least one titanium-derived compound in an amount which is equivalent to from approximately 10 ppm to approximately 10,000 ppm of fluorine.

7. (Amended) A composition for buccal use according to Claim 5 wherein it is in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution.

8. (Amended) A composition for buccal use according to Claim 5 wherein it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by weight with respect to the total weight of the composition.

9. (Amended) A composition for buccal use according to Claim 8, wherein the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

10. (Amended) A composition for buccal use according to Claim 5 wherein it also comprises one or more cohesion agents, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition, chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or carrageenan gums, synthetic carrageenates, and synthetic thickeners such as cellulose

derivatives for instance the sodium salt of carboxymethylcellulose, methylcellulose, hydroxyalkylcelluloses or crosslinked polyacrylic acids.

11. (Amended) A composition for buccal use according to Claim 5 wherein it also comprises one or more surfactants of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

12. (Amended) A composition for buccal use according to Claim 5 wherein it also comprises one or more active agents used in buccal hygiene, in particular agents known to reduce bad breath, such as for example chlorhexedine, cetylpyridinium chloride, cyclodextrins or zinc compounds such as zinc halides, zinc acetate, zinc citrate or zinc fluoride.

13. (Amended) A composition for buccal use according to Claim 5 wherein it also comprises one or more cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes, aromas, flavourings and flavour-enhancing substances, plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active on the gums, anti-inflammatory agents such as enoloxone, benzydamine, allantoin or permethol.

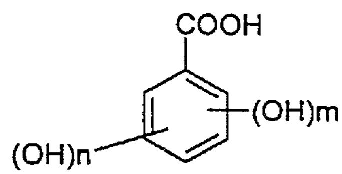
14. (Amended) A composition ~~Compositions~~ for buccal use according to Claim 13, ~~characterized in that~~ wherein the sweetening agents comprise sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizinates, alpha-glucosyl/ steviolglucoside mixtures, D-mannitol, aspartame, acesulfame K, sorbitol, lycosin and mixtures thereof.

15. (Amended) A composition for buccal use according to Claim 13, wherein the antibacterial agents comprise essential oils, plant extracts or substances such as alexidine, octinidine, hexetidine, phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition.

16. (Amended) A method of protecting against dental caries which comprises administering a titanium-derived compound satisfying the formula (I) below:

$[TiF_xL_y]^{z-}$ (I)

in which L represents a compound of formula (II) below:



(II)

in which m is 0 or 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts~~, as protecting agent against dental caries~~.

Please add the following new claims:

17. (New) A method for preparing a titanium-derived compound according to Claim 2, wherein solid titanium IV fluoride is reacted with a solution of benzoic acid in an anhydrous solvent such as acetonitrile, under a nitrogen atmosphere.

18. (New) A method for preparing a titanium-derived compound according to Claim 3, wherein solid titanium IV fluoride is reacted with a solution of benzoic acid in an anhydrous solvent such as acetonitrile, under a nitrogen atmosphere.

19 (New) A composition for buccal use according to Claim 6, wherein it is in the form of toothpaste or toothgeel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution.

20. (New) A composition for buccal use according to Claim 6, wherein it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by weight with respect to the total weight of the composition.

21. (New) A composition for buccal use according to Claim 7, wherein it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by weight with respect to the total weight of the composition.

22. (New) A composition for buccal use according to Claim 19, wherein it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by weight with respect to the total weight of the composition.

23. (New) A composition for buccal use according to Claim 20, wherein the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

24. (New) A composition for buccal use according to Claim 21, wherein the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

25. (New) A composition for buccal use according to Claim 22, wherein the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular

trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

26. (New) A composition for buccal use wherein it comprises a compound according to Claim 2.

27. (New) A composition for buccal use wherein it comprises a compound according to Claim 3.

28. (New) A method of protecting against dental carries which comprises administering a compound according to claim 2.

29. (New) A method of protecting against dental carries which comprises administering a compound according to claim 3.

REMARKS

Claims 1-16 have been amended in order to write these claims in the appropriate U.S. claim format.

Claims 4, 7-8, and 10-13 have also been amended in order to limit the multiple dependencies of these claims.

Claims 17-29 have been added by the foregoing amendments. Support for claims 17-18 occurs, for example, in original claim 4. Support for claim 19 occurs, for example, in original claim 7. Support for claims 20-22 occurs, for example, in original claim 8. Support for claims 23-25 occurs, for example, in original claim 9. claims 26 and 27 are simply the corresponding composition claims for the compounds of claims 2-3. Claims 28-29 are simply the corresponding method claims for the compounds of claims 2-3.

Claims 1-29 remain in the application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Date: January 14, 2002

Michael D. Alexander
Reg. No. 36,080

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Version With Markings to Show Changes Made

In the Specification:

The following Abstract of the disclosure has been provided as a new page 24:

ABSTRACT

The invention relates to a titanium-derived compounds, and to processes for preparing the same.

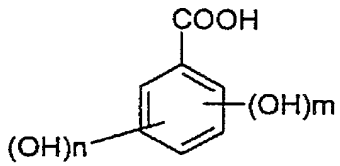
In the Claims:

Claims 1-16 have been amended as follows:

1. (Amended) A titanium~~Titanium~~-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:

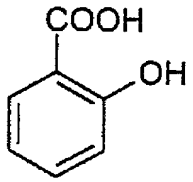


(II)

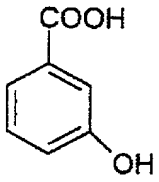
in which m is 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

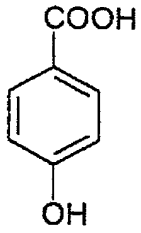
2. (Amended) A compound ~~Compound~~ according to Claim 1, ~~characterized in that~~ wherein the compounds L are chosen from benzoic acid derivatives, in particular 2-hydroxybenzoic acid of formula:



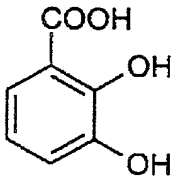
3-hydroxybenzoic acid of formula:



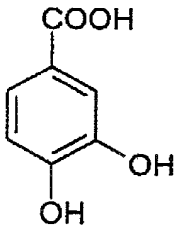
4-hydroxybenzoic acid of formula:



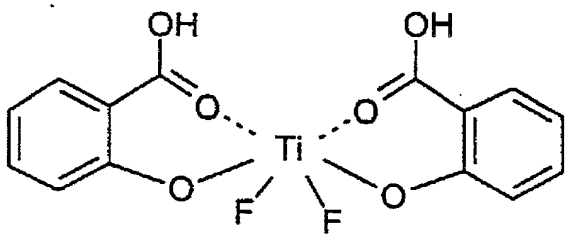
2,3-dihydroxybenzoic acid of formula:



3,4-dihydroxybenzoic acid of formula:



3. (Amended) A compound ~~Compound~~ according to Claim 1, ~~characterized in that~~ wherein it satisfies the formula below (III):



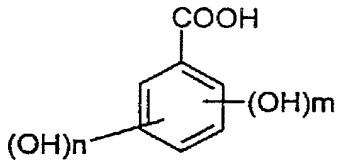
(III)

4. (Amended) A method ~~Method~~ for preparing a titanium-derived compound according to Claim 1 ~~any one of Claims 1 to 3, characterized in that~~ wherein solid titanium IV fluoride is reacted with a solution of benzoic acid in an anhydrous solvent such as acetonitrile, under a nitrogen atmosphere.

5. (Amended) A composition ~~Composition~~ for buccal use, ~~characterized in that~~ wherein it comprises at least one titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

in which m is 0, 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

6. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~characterized in that~~ wherein it comprises at least one titanium-derived compound in an amount which is equivalent to from approximately 10 ppm to approximately 10,000 ppm of fluorine.

7. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~either of Claims 5 and 6, characterized in that~~ wherein it is in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm,

paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution.

8. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~any one of Claims 5 to 7, characterized in that~~ wherein it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by weight with respect to the total weight of the composition.

9. (Amended) A composition ~~Composition~~ for buccal use according to Claim 8, ~~characterized in that~~ wherein the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

10. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~any one of Claims 5 to 9, characterized in that~~ wherein it also comprises one or more cohesion agents, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition, chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or carrageenan gums, synthetic carrageenates, and synthetic thickeners such as cellulose derivatives for instance the sodium salt of carboxymethylcellulose, methylcellulose, hydroxyalkylcelluloses or crosslinked polyacrylic acids.

11. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~any one of Claims 5 to 10, characterized in that~~ wherein it also comprises one or more surfactants of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

12. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~any one of Claims 5 to 11, characterized in that~~ wherein it also comprises one or more active agents used in buccal hygiene, in particular agents known to reduce bad breath, such as for example chlorhexedine, cetylpyridinium chloride, cyclodextrins or zinc compounds such as zinc halides, zinc acetate, zinc citrate or zinc fluoride.

13. (Amended) A composition ~~Composition~~ for buccal use according to Claim 5 ~~any one of Claims 5 to 12, characterized in that~~ wherein it also comprises one or more cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes, aromas, flavourings and flavour-enhancing substances,

plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active on the gums, anti-inflammatory agents such as enoloxone, benzydamine, allantoin or permethol.

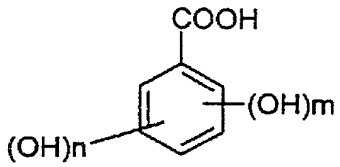
14. (Amended) A composition ~~Compositions~~ for buccal use according to Claim 13, ~~characterized in that~~ wherein the sweetening agents comprise sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizinates, alpha-glucosyl/ steviolglucoside mixtures, D-mannitol, aspartame, acesulfame K, sorbitol, lycosin and mixtures thereof.

15. (Amended) A composition ~~Composition~~ for buccal use according to Claim 13, ~~characterized in that~~ wherein the antibacterial agents comprise essential oils, plant extracts or substances such as alexidine, octinidine, hexetidine, phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition.

16. (Amended) ~~Use of~~ A method of protecting against dental caries which comprises administering a titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

in which m is 0 or 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts~~, as protecting agent against dental caries~~.

Claims 17-29 have been added.

ENGLISH TRANSLATION OF INTERNATIONAL PATENT
APPLICATION PCT/FR00/01994
filed on 11 July 2000

CERTIFICATE UNDER 37 C.F.R. 1.10

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Washington, DC 20231

Signature

TITANIUM COMPOUNDS, PREPARATION AND USE THEREOF

The invention relates to novel titanium-derived compounds, as well as to the preparation thereof.

The invention also relates to compositions for buccal use comprising such titanium-derived compounds.

It is known that titanium tetrafluoride (TiF_4) can bind to the surface of the tooth, forming an amorphous protective layer, also termed glaze, at the surface of the enamel of the tooth.

The formation of such a protective layer at the surface of the tooth has led to envisage the use of titanium tetrafluoride as an agent for preventing and for treating dental caries.

Titanium tetrafluoride has however the drawback of being highly acidic in aqueous solution (pH of about 1.5), which is aggressive for the tissues mineralized and not compatible with physiological pHs.

Its use in preventing dental caries has thus been limited, so far, to professional use with a very short application time, followed by rinsing.

Titanium tetrafluoride also has the drawback of being relatively unstable, in particular in aqueous solution.

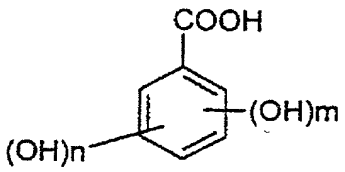
The aim of the invention is to remedy these drawbacks by providing titanium IV-derived compounds

comprising fluorine which are capable of forming a glaze at the surface of the tooth, and which can be used in aqueous solution and at physiological pHs varying from approximately 6.5 to approximately 7.5.

The titanium-derived compounds according to the invention satisfy the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

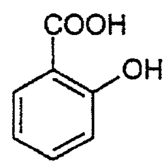
in which m is 0 or 1 and n is 0, 1 or 2,
and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2.

The compounds of formula (I) can comprise one or more asymmetrical carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. These enantiomers and diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, form part of the invention.

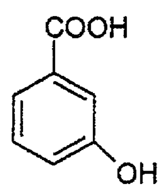
The compounds of the present invention can exist in the form of free bases or of addition salts to

pharmaceutically acceptable acids. All these forms form part of the invention.

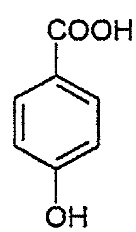
According to the invention, compounds L which can be used are in particular benzoic acid derivatives, in particular 2-hydroxybenzoic acid of formula:



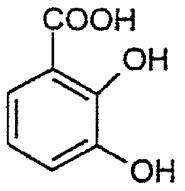
, 3-hydroxybenzoic acid of formula:



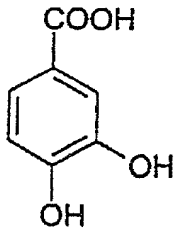
, 4-hydroxybenzoic acid of formula:



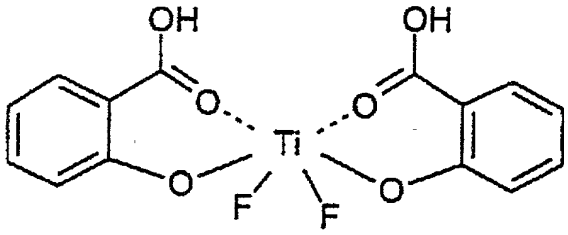
, 2,3-dihydroxybenzoic acid of formula:



, 3,4-dihydroxybenzoic acid of formula:



An example of a titanium-derived compound according to the invention is the compound represented by the formula below (III):



(III)

The titanium(IV)-derived compounds of the invention can be prepared by reacting, at room temperature, solid titanium IV fluoride with a solution of benzoic acid in an anhydrous solvent such as

acetonitrile, under a nitrogen atmosphere.

The starting products are commercially available or described in the literature, or can be prepared by methods which are described therein or which are known to persons skilled in the art.

The invention is also directed towards protecting compositions for buccal use comprising at least one compound according to the invention, and also the use of the titanium-derived compounds according to the invention, as a protecting agent against dental caries.

The compositions of the invention comprise at least one compound according to the invention in an amount which is equivalent to from approximately 10 ppm to approximately 10,000 ppm of fluorine, and which is calculated from the molecular weight of the compound according to the invention.

The compositions of the invention can be in the usual diverse forms for compositions for buccal use, and in particular in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution, the vehicle therefore being chosen depending on the form of use desired.

The compositions of the invention can

contain, in addition to the titanium-derived compound(s), by way of vehicle or for their intrinsic activity, excipients or ingredients usually used in compositions for buccal use.

The compositions of the invention are prepared according to the usual methods which correspond to the vehicles chosen. The physiologically acceptable vehicle can be different in nature depending on the form chosen for the composition: aqueous solution, thickened or unthickened aqueous-alcoholic solution, gum, pasty or solid excipient, etc.

According to the forms desired, the compositions of the invention can also comprise at least one polishing agent in proportions ranging up to 80% by weight with respect to the total weight of the composition. The polishing agents are for example of inorganic or organic origin. Their nature may differ according to the vehicle used for the chosen form.

Polishing agents which can be used comprise calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium or calcium oxides, hydroxides, trisilicates and pyrophosphates, or cellulose compounds obtained by crushing cereal seeds for example.

When the compositions are in the form of toothpaste, they can contain a polishing agent in

proportions generally of between approximately 2% and approximately 70% by weight, preferably of between approximately 15% and approximately 25% by weight. It is generally an inorganic abrasive polishing agent consisting of one or more compounds which are, for the most part, insoluble in water. By way of examples, mention may be made of sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, silicas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate, and calcium or sodium carbonates and bicarbonates.

The compositions of the invention which are in the form of toothpaste can also comprise one or more cohesion agents. Such cohesion agents can be incorporated in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition, and preferably of between approximately 0.5% and approximately 3% by weight. The cohesion agents can be chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or carrageenan gums, and synthetic thickeners such as cellulose derivatives for instance the sodium salt of carboxymethylcellulose, methycellulose,

hydroxyalkylcelluloses, crosslinked polyacrylic acids or synthetic carrageenates.

According to certain embodiments, the compositions of the invention can comprise one or more sufficiently stable and foam-forming surfactants. The surfactants which can be used may be of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

Generally, the surfactants are present in the compositions of the invention in a weight range which varies from approximately 0.01% to approximately 4%, preferably from approximately 0.1% to approximately 2%, with respect to the total weight of the composition.

In addition, the compositions of the invention can comprise other active agents which are used in buccal hygiene, in particular agents known to reduce bad breath, such as for example cyclodextrins or zinc compounds such as for example zinc halides, zinc acetate, zinc citrate or zinc fluoride, chlorhexedine or cetylpyridinium chloride.

The compositions of the invention can also comprise diverse cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes, aromas, flavourings and flavour-enhancing substances, plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active

on the gums, anti-inflammatory agents such as enoloxone, benzydamine, allantoin, permethol, etc.

These various agents are present in the compositions of the invention according to the form of use.

Thus, when the composition for buccal use is a spray, the vehicle can be an aqueous-alcoholic solution, and the composition can also comprise aromas, peptizing agents, and sweetening, wetting or refreshing agents.

When the composition for buccal use is in the form of mouthwash, the vehicle can be nonaqueous, aqueous or aqueous-alcoholic with one or more surfactants and/or one or more thickeners, and can also comprise bactericidal agents, sweetening agents and flavourings.

By way of example, when the composition is in the form of dental gel, it can also comprise agents which are active on the gums.

When the composition is in the form of chewing gum, it comprises at least one natural or synthetic chewable gum, and can also comprise plasticizers, vitamins, flavourings or flavour enhancers, sweeteners, wetting agents, bactericides, preserving agents, dyes.

Among the chewable gums which can be used are in particular hevea latex, chicle gum, schlong gum,

polyvinyl acetate and synthetic elastomers, in particular silicone rubber, butyl rubber and the derivatives and/or mixtures thereof.

The compositions for buccal use of the invention can also comprise a sweetening agent. Among the sweetening agents which can be used, mention may be made of sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizinates, alpha-glucosyl/ steviolglucoside mixtures, D-mannitol, aspartame, acesulfame K, sorbitol, lycosin and mixtures thereof.

The sweetening agents are generally present in an amount ranging up to approximately 2% by weight with respect to the total weight of the composition.

As wetting agents, mention may be made of sorbitol, glycerol or xylitol, which are present as such in concentrations which can reach 70% by weight.

In addition, refreshing agents such as menthol or ethylmaltol can be incorporated into the compositions of the invention.

It is also possible to use preserving agents, which are chosen from in particular methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium benzoate and chlorhexedine, at concentrations generally of approximately 1% by weight or lower.

The flavourings which can be used comprise all those which are authorized as such in the food

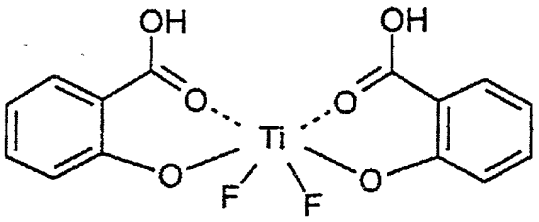
trade. For example, mention may be made of mint, aniseed, eucalyptus, cinnamon, clove, sage and liquorice essences, and fruit essences such as orange, lemon, mandarin or strawberry. The flavourings are generally present in an amount by weight of approximately 5% or less.

The compositions of the invention can also comprise an antibacterial agent chosen preferably from in particular essential oils, plant extracts or substances such as cetylpyridinium chloride, alexidine, octinidine, hexetidine, phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition.

The example which follows illustrates the preparation of a titanium-derived compound of the invention. The elemental microanalyses and the I.R. and N.M.R. spectra confirm the structure of the compound obtained.

Example 1.

Preparation of the compound of formula (III):



(III)

5 g (0.040 mol) of solid titanium fluoride are added to 10 g (0.072 mol) of a salicylic acid solution in 100 ml of anhydrous acetonitrile with stirring and under nitrogen. The reaction mixture rapidly turns an orange colour, and the solution is left to stir for 24 hours. After decantation and concentration by evaporating off, the solution is cooled overnight and small needle crystals form which correspond to the salicylic acid which has not reacted. The solution is refiltered, concentrated and cooled to 4°C to give small yellow/orangey monoclinic crystals. After filtration and drying under vacuum, the compound of formula (III) is obtained with a yield of approximately 49%.

Melting point: 157-160°C (decomposition)

The compounds of the invention have been the subject of biological studies which have demonstrated their properties of forming a glaze at the surface of the tooth and their value as substances for treating or preventing dental caries.

A fresh tooth sample is placed in a glass phial containing moist cotton and thymol at a temperature of +4°C.

The sample is cleared of soft tissues possibly present on the tooth. The tooth is then polished in a rubber dish containing pumice stone free

of fluoride, and then rinsed in an ultrasonic bath. The sample is treated with an aqueous solution of compound (III) of the invention, at pH 5, for 10 minutes at 37°C. The sample is then washed with water for one minute and a window made at the surface of the tooth is observed by microscopy.

The formation of an amorphous protective layer on the surface of the tooth after treatment of the sample with compound (III) is demonstrated.

The results of these biological tests show that the compounds of the invention exhibit properties of forming a protective glaze on the surface of the tooth.

They can be used in treating and preventing dental caries.

Examples of compositions of the invention are given below.

<u>Formulation for toothpaste</u>.

Ingredient	Amount
Titanium compound	q.s. 2500 ppm of F
Permethol	0.250 g
70% sorbitol	25.00 g
Precipitated silicas	18.00 g
Sodium lauryl sulphate	2.00 g
Sodium carrageenate	1.00 g
Titanium oxide	1.00 g
Mint aroma	0.950 g

Gesweet	0.100 g
Parabens	0.400 g
Water	q.s. 100,00 g

Formulation for toothpaste.

Ingredient	Amount
Titanium compound	q.s. 1500 ppm of F
Chlorhexidine digluconate	0.125 g
Vitamin E acetate	0.5 g
70% sorbitol	28.00 g
Precipitated silicas	11.00 g
Sodium lauryl sulphate	0.750 g
Chimexane NF	0.750 g
Sodium carboxymethylcellulose	1.300 g
Mint aroma	1.00 g
Sodium saccharinate	0.150 g
Titanium oxide	1.00 g
Parabens	0.300 g
Phosphate dodecahydrate	0.070 g
Water	q.s. 100.00 g

Formulation for mouthwash.

Ingredient	Amount
Titanium compound	q.s. 250 ppm of F
Sodium 4-methylesculetol monoethoxide	1 g
D-panthenol	5 g
Cremophor RH 410	0.5 g
95% (V/V) alcohol	80 g

Gesweet	1 g
Mint aroma	0.795 g
Patent blue	0.004 g
Purified water	q.s. 1 000 g

<u>Formulation for mouthwash</u>.

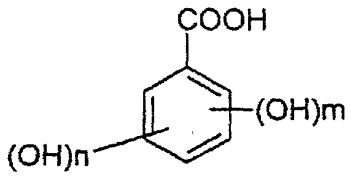
Ingredient	Amount
Titanium compound	q.s. 250 ppm of F
Sodium benzoate	0.4 g
95% (V/V) alcohol	10.00 g
Sodium saccharinate	0.005 g
Benzoic acid	0.100 g
Menthol aroma	0.035 g
Levomenthol	0.010 g
Dyes	0.0012 g
Water	q.s. 100,00 g

CLAIMS

1. Titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

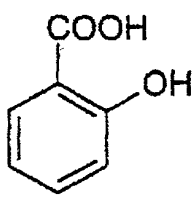
in which L represents a compound of formula (II) below:



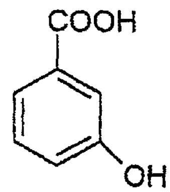
(II)

in which m is 1 and n is 0, 1 or 2,
and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

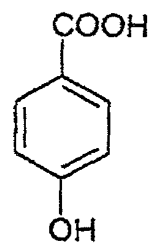
2. Compound according to Claim 1, characterized in that the compounds L are chosen from benzoic acid derivatives, in particular 2-hydroxybenzoic acid of formula:



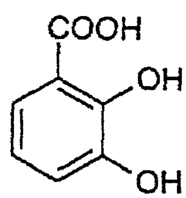
, 3-hydroxybenzoic acid of formula:



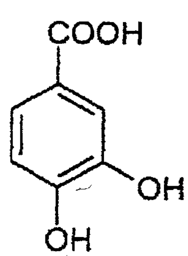
, 4-hydroxybenzoic acid of formula:



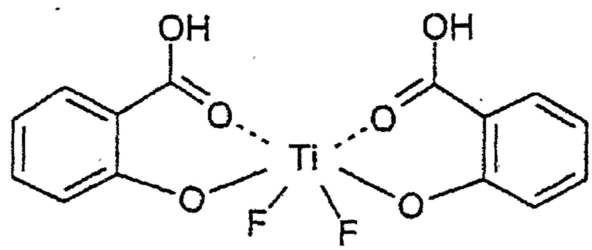
, 2,3-dihydroxybenzoic acid of formula:



, 3,4-dihydroxybenzoic acid of formula:



3. Compound according to Claim 1, characterized in that it satisfies the formula below (III):



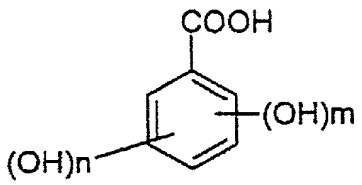
(III)

4. Method for preparing a titanium-derived compound according to any one of Claims 1 to 3, characterized in that solid titanium IV fluoride is reacted with a solution of benzoic acid in an anhydrous solvent such as acetonitrile, under a nitrogen atmosphere.

5. Composition for buccal use, characterized in that it comprises at least one titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

in which m is 0, 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts.

6. Composition for buccal use according to Claim 5, characterized in that it comprises at least one titanium-derived compound in an amount which is equivalent to from approximately 10 ppm to approximately 10,000 ppm of fluorine.

7. Composition for buccal use according to either of Claims 5 and 6, characterized in that it is in the form of toothpaste or toothgel, of mouthwash, of spray, of foam, of gargling product, of dental gel or of chewing gum, balm, paste, glaze, lozenge, tablet, antiseptic throat preparation, powder, or concentrated or unconcentrated solution.

8. Composition for buccal use according to any one of Claims 5 to 7, characterized in that it also comprises at least one polishing agent of inorganic or organic origin in proportions ranging up to 80% by

weight with respect to the total weight of the composition.

9. Composition for buccal use according to Claim 8, characterized in that the polishing agent comprises in particular calcium, magnesium or sodium carbonate or bicarbonate, calcium phosphates and sulphates, alumina and hydrated alumina, silicas, magnesium oxides, hydroxides, trisilicates and pyrophosphates, cellulose compounds obtained by crushing cereal seeds, sodium or potassium metaphosphates, calcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, alumina, hydrated, and in particular trihydrated, aluminas, aluminium or zirconium silicates, bentonite, as well as magnesium orthophosphate or trimagnesium phosphate.

10. Composition for buccal use according to any one of Claims 5 to 9, characterized in that it also comprises one or more cohesion agents, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition, chosen in particular from natural thickeners such as alginates or pectins, natural gums such as gum tragacanth or xanthan, guar, carob or carrageenan gums, synthetic carrageenates, and synthetic thickeners such as cellulose derivatives for instance the sodium salt of carboxymethylcellulose, methylcellulose,

hydroxyalkylcelluloses or crosslinked polyacrylic acids.

11. Composition for buccal use according to any one of Claims 5 to 10, characterized in that it also comprises one or more surfactants of anionic, amphoteric, zwitterionic, cationic or nonionic nature.

12. Composition for buccal use according to any one of Claims 5 to 11, characterized in that it also comprises one or more active agents used in buccal hygiene, in particular agents known to reduce bad breath, such as for example chlorhexedine, cetylpyridinium chloride, cyclodextrins or zinc compounds such as zinc halides, zinc acetate, zinc citrate or zinc fluoride.

13. Composition for buccal use according to any one of Claims 5 to 12, characterized in that it also comprises one or more cohesion agents, thickeners, antibiotics, sweetening, wetting or refreshing agents, peptizing agents, preserving agents, sweeteners, dyes, aromas, flavourings and flavour-enhancing substances, plasticizers, antibacterial agents or bactericides, vitamins, antitartar agents, healing agents, vasomotor agents, anti-bleeding agents, agents which are active on the gums, anti-inflammatory agents such as enoloxone, benzydamine, allantoin or permethol.

14. Compositions for buccal use according to Claim 13, characterized in that the sweetening agents

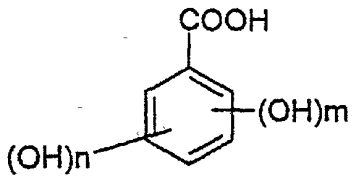
comprise sucrose, lactose, fructose, xylitol, sodium cyclamate, sodium saccharinate or maltose, sodium or ammonium glycyrrhizinates, alpha-glucosyl/ steviolglucoside mixtures, D-mannitol, aspartame, acesulfame K, sorbitol, lycosin and mixtures thereof.

15. Composition for buccal use according to Claim 13, characterized in that the antibacterial agents comprise essential oils, plant extracts or substances such as alexidine, octinidine, hexetidine, phenoxyethanol, phenethyl alcohol, triclosan, chlorhexidine, cetylpyridinium chloride and delmopinol, in proportions ranging up to approximately 10% by weight with respect to the total weight of the composition.

16. Use of a titanium-derived compound satisfying the formula (I) below:

$$[TiF_xL_y]^{z-} \qquad (I)$$

in which L represents a compound of formula (II) below:



(II)

in which m is 0 or 1 and n is 0, 1 or 2,

and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2; in the form of enantiomers, of diastereoisomers, as well as the mixtures thereof, including the racemic mixtures, of free bases or of pharmaceutically acceptable salts, as protecting agent against dental caries.

ABSTRACT

he invention relates to a titanium-derived compounds, and to processes for preparing the same.

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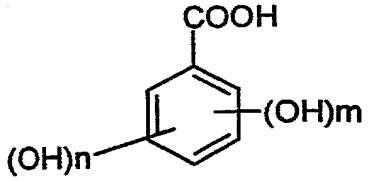
En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

(54) Title: TITANIUM DERIVED COMPOUNDS, PREPARATION AND USE THEREOF

(54) Titre: COMPOSES DE TITANE, LEUR PREPARATION ET UTILISATION



(II)

(57) Abstract: The invention concerns compounds derived from titanium of formula $[TiF_xL_y]^{z-}$ wherein L represents a compound of formula (II): wherein m is 0 or 1 and n is 0, 1 or 2, and x represents 2, 4 or 5, y represents 1 or 2 and z represents 0, 1 or 2. The invention also concerns the use of said compounds in compositions for oral use, for preventing dental decay.

(57) Abrégé: L'invention se rapporte à des composés dérivés de titane de formule $[TiF_xL_y]^{z-}$ dans laquelle L représente un composé de formule (II) dans laquelle m est 0 ou 1 et n est 0, 1 ou 2, et x représente 2, 4 ou 5, y représente 1 ou 2 et z représente 0, 1 ou 2. L'invention se rapporte également à l'utilisation de ces composés dans des compositions à usage buccal, en vue de prévenir la formation de la carie dentaire.

Attorney Docket No. SANSYL006/PM

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

__X__ Original _____ Supplemental _____ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and mailing address are given below under my name.

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITANIUM DERIVED COMPOUNDS, PREPARATION AND USE THEREOF

the application for which

___ is attached hereto.

___ was filed on _____ as United States
Application Serial No. _____
and was amended on _____ (if applicable)

___ was filed on 11 July 2000 as PCT International
Application No. PCT/FR00/01994
and was amended on _____ (if applicable)

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in Section 1.56 of Title 37 of the Code of Federal Regulations, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I/We hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

Country	Number	Filing Date	Priority Claimed Yes	Priority Claimed No
FRANCE	99 09194	16 July 1999	X	

Attorney Docket No. SANSYL006/PM

I/We hereby claim benefit under Section 119(e) of Title 35 of the United States Code of any United States provisional application(s) identified below:

Application No.	Filing Date

I/We hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT international application(s) designating the United States identified below:

Application Serial No.	Filing Date	Status

I/We hereby appoint Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my/our attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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I/We hereby declare that all statements made herein and in the above-identified application of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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